

Rapidly progressive lung disease in a patient with cystic fibrosis on long-term azithromycin: possible role of mycoplasma infection

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Abstract

Macrolides is effective therapy in patients with cystic fibrosis (CF). We describe a girl with CF given long-term azithromycin who died of rapidly progressive lung disease. She was found to have rising titers of mycoplasma serology, suggesting a possible causative role of a resistant mycoplasma infection. Mycoplasma infection should be considered in CF patients who are deteriorating, even if they are being treated with macrolides, to which these organisms are usually susceptible.

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1. Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disease among Caucasian population. It has been reported among almost all ethnic groups including Arabs [1]. Recently, the cystic fibrosis transmembrane regulator (CFTR) gene mutation I1234V on exon 19 has been identified as the main genotype of CF among large kindred of Bedwens from Qatar [2].

The macrolide antibiotics have been of interest in CF for more than their well-established antibacterial properties [3]. This interest started after observing dramatic improvements with the use of low dose erythromycin in diffuse panbronchiolitis, a disease very similar to CF occurring in middle-aged people from the Far East especially Japan. Recently, the macrolide azithromycin has been studied in a randomized, placebo-controlled crossover trial in children with CF

[4]. Subjects who received azithromycin showed significant clinical improvement [4]. In another study, azithromycin therapy was evaluated in 60 adults with CF. The azithromycin group had better quality of life, maintained better pulmonary function, had fewer courses of intravenous antibiotic use and had lower CRP as compared with the placebo group [5]. Based on these studies, their use has been advocated in CF.

We report on a girl with CF who despite being treated with azithromycin for about 8 months, who developed severe progressive lung disease, with evidence suggestive of persistent infection with *Mycoplasma pneumoniae*.

2. Case report

SH was an 18-year-old Arabian girl from Qatar who was diagnosed with CF at age 8 years when she presented with recurrent pulmonary infections. She had two elevated sweat chloride test levels (68 and 87 mmol/L). Her genotype was confirmed to be homozygous for I1234V on exon 19.

She was pancreatic insufficient and was maintained on pancreatic enzymes replacement therapy. At the time

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25–75%}, forced expiratory flow between 25–75% of flow–volume curve.

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of diagnosis she had mild lung disease (FVC=81%, FEV₁=83%, FEF_{25–75%}=74% predicted) (Fig. 1). She was started on azithromycin 250 mg orally once a day in January 2002. At that point her spirometric measures were: FVC=63%, FEV₁=65% and FEF_{25–75%}=54% predicted. Initially, she did well but five months later she was admitted with an acute pulmonary exacerbation. Her weight was below the 5% for age with a BMI of 14; she had advanced clubbing. Her pulmonary function testing showed a sharp drop in spirometry to FVC=43%, FEV₁ 41% and FEF_{25–75%}=30% predicted. Her sputum grew mucoid *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenza*. All of these bacteria were sensitive to the antibiotic regimen that she was receiving (namely: ceftazidime, gentamicine and cloxacillin). At that point mycoplasma antibody titre was 1:1280 (positive) she was started on clarythromycin and azithromycin was discontinued.

Patient's serum was tested using serodia Myco II (Fujirebio Inc., Tokyo, Japan) particle-agglutination test kit for detection of anti-*M. pneumoniae* antibody [6]. The kit uses artificial gelatin particles, sensitized with cell membrane components of *M. pneumoniae* (Mac strain). The test is based on the principle that sensitized particles are agglutinated by the presence of antibody to *M. pneumoniae* in patient serum. Colored artificial carrier is used which produces more clear-cut and easy-to-read agglutination patterns compared with hemagglutination patterns. Positive and negative controls are included in each run. The end antibody titer is determined as the final dilution giving positive pattern. Specimen showing positive at 1:40 dilution or more with sensitized particles is interpreted as positive.

She improved slightly after 3 weeks on clarythromycin but her spirometry was unchanged (FVC=44%, FEV₁=48% and FEF_{25–75%}=34% predicted) and she became oxygen dependant at home. She was readmitted a month later in moderate distress with increased oxygen requirement. Her

spirometry at that point showed a further drop (FVC=30%, FEV₁=28%, FEF_{25–75%}=14% predicted) (Fig. 1). A repeat mycoplasma antibody titre was positive at 1:6200. Her sputum continued to grow the same microorganisms but was not specifically cultured for mycoplasma species (mycoplasma cultures are not done in our laboratory). She was re-started on clarythromycin, however, without significant improvement. She continued to deteriorate and died a week later.

3. Discussion

We report this case for two reasons; firstly, although one possible reason for beneficial effect of macrolides has been proposed to be treatment of occult atypical infection, she developed Mycoplasma Pneumonia during the course of macrolide therapy. We assume that her high mycoplasma (particle agglutination) titer was due to a persistent and recent mycoplasma infection. The test insert claims 86% sensitivity and 83% specificity. Some other organisms might cross-react with mycoplasma CFT e.g. Legionella, Q-fever and Chlamydia infections; the particle agglutination test has much less cross reactivity problem than other serological tests. However, it must be acknowledged that specific testing for some of these other infections might have been helpful. The fact that her titres increased on her second admission argues for a recent and possibly persistent mycoplasma infection.

Suspicion of *M. pneumoniae* infection is usually based on serological studies (either ELISA or CFT), however, to confirm the diagnosis, mycoplasma culture is necessary. Most laboratories—including that of our institute—do not routinely culture for *M. pneumoniae*. In addition, methods for PCR diagnosis *M. pneumoniae* are yet to be validated and are not generally available.

Macrolide resistance in *M. pneumoniae* is not well described and the mechanism is unknown. The benefit from long-term treatment of CF patients with azithromycin is an empirical observation that becomes evident after several months' therapy [4]. The mechanism of this benefit is unknown and hypotheses include an anti-inflammatory mechanism. The development of resistant strains of *M. pneumoniae* because of long-term use of macrolides is unknown. Although we do not have antibiotic susceptibilities, it seems likely that a macrolide resistant strain of *M. pneumoniae* was selected by this therapy; to our knowledge, a similar case has not been reported before.

The second reason for reporting this case is to highlight the possible role of non-typical CF organisms in the deteriorating patient. The long-term use of macrolide antibiotics has resulted in significant improvements in patients with diffuse panbronchiolitis. They are currently recommended for CF patients not doing well on conventional treatments based on large clinical trials [4,5] and yet unpublished USCF data (personal communication). Empir-

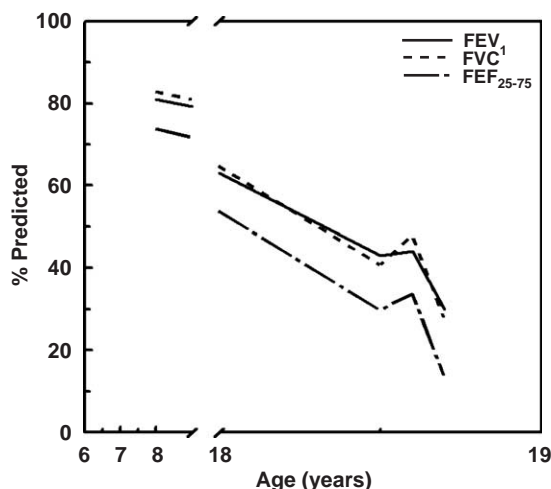


Fig. 1. Deterioration in FEV₁, FVC and FEF_{25–75%} over time.

ically, some clinicians use them in cases of chronic bronchiectasis secondary to a variety of etiologies.

Although SH was chronically colonized with the “usual” CF bacteria in her sputum, we speculate that development of resistant strains of mycoplasma species might have played a significant role in her rapid deterioration and death. In support of this view is the fact that the bacteria isolated from sputum were all sensitive to the antibiotic regimen that she was treated with. In addition, her sputa failed to grow any of the more recently described “new CF organisms” [atypical mycobacteria, *B. Cepacia*, *Alcaligenes*] that might explain the late clinical deterioration.

Although macrolide antibiotics have proved to be effective in cases of diffuse panbronchiolitis and are advocated in CF, the possible adverse effects of long-term use in CF need to be further studied.

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